

## Summary Of Differences Between The Prior Art And The Claimed Invention Of 09/992,107

<p><b><u>Hager (EP 0470437) (1992)</u></b></p> <ul style="list-style-type: none"> <li>• Hager discloses liposomes with a mean diameter between 50-180 nm and 70-130 nm.</li> <li>• Example 3 discloses liposomes with a mean diameter of 129 nm bound to propidium iodide (a DNA marker and mutagen).</li> </ul>	<ul style="list-style-type: none"> <li>• Hager does not disclose a pharmaceutically acceptable drug free liposome preparation having the claimed Gaussian distribution.</li> <li>• Example 3, the only disclosure of liposomes arguably within the claimed distribution, is not pharmaceutically acceptable.</li> </ul>
<p><b><u>Braun (EP 0461559)</u></b></p> <ul style="list-style-type: none"> <li>• Braun discloses unilamellar liposomes having an average diameter of: <ul style="list-style-type: none"> <li>• 500 nm - "several microns" (p. 1, l. 15*);</li> <li>• 60-500 nm (p. 1, l. 17);</li> <li>• 20-200 nm (p. 2, l. 12);</li> <li>• 200 nm (p. 11, l. 24;</li> <li>• below 200 nm (p. 10, l. 8);</li> <li>• 50-120 nm (p. 2, l. 25);</li> <li>• below 120 nm (p. 11, ll. 20-21);</li> <li>• 50-80 nm (p. 2, l. 26);</li> <li>• 20-50 nm (p. 1, l. 16);</li> <li>• 60 nm (p. 10, l. 11);</li> </ul> </li> <li>• Braun teaches that the most effective liposomes are 60 nm (even though LDL increases). Data is limited to animal experiments.</li> </ul> <p>* (citations are to the English translation)</p>	<ul style="list-style-type: none"> <li>• Braun does not disclose a pharmaceutically acceptable liposome preparation having the claimed Gaussian distribution.</li> </ul>

<p><u>Williams 1984 [Williams et al., <i>Intravenously Administered Lecithin Liposomes: A Synthetic Antiatherogenic Lipid Particle</i>, 27.3 PERSPECTIVES IN BIOLOGY AND MEDICINE 417-431 (1984)]</u></p> <ul style="list-style-type: none"> <li>Williams 1984 discloses lecithin liposomes for mobilizing cholesterol and treating atherosclerosis having diameters of 30-60 nm (page 422, ll. 41-43 and page 425, ll. 41-44). Liposomes of 21-50 nm prepared by "vigorous agitation or, more effectively, by ultrasonic irradiation" are also disclosed (p. 419, l. 22).</li> </ul>	<ul style="list-style-type: none"> <li>Williams 1984 does not disclose a pharmaceutically acceptable liposome preparation having the claimed Gaussian distribution.</li> </ul>
<p><u>Williams 1986 [Williams et al., <i>Uptake of Endogenous Cholesterol by a Synthetic Lipoprotein</i>, 875 BIOCHIMICA BIOPHYSICA ACTA 183-94 (1986)]</u></p> <ul style="list-style-type: none"> <li>Williams 1986 discloses liposomes that are small unilamellar vesicles that are used in animals and <i>in vitro</i> human blood samples.</li> </ul>	<ul style="list-style-type: none"> <li>Williams 1986 does not disclose a pharmaceutically acceptable liposome preparation having the claimed Gaussian distribution.</li> </ul>
<p><u>Williams 1988 [Williams et al., <i>Low Density Lipoprotein Receptor-Independent Hepatic Uptake of a Synthetic, Cholesterol-Scavenging Lipoprotein: Implications For The Treatment of Receptor-Deficient Atherosclerosis</i>, 85 Proc. Natl. Acad. Sci. 242-46 (1988)]</u></p> <ul style="list-style-type: none"> <li>Williams 1988 discloses liposomes that are small unilamellar vesicles that are used in animals.</li> </ul>	<ul style="list-style-type: none"> <li>Williams 1988 does not disclose a pharmaceutically acceptable liposome preparation having the claimed Gaussian distribution.</li> </ul>

**Rodrigueza '93 [Rodrigueza et al., *The Influence of Size and Composition On the Cholesterol Mobilizing Properties Of Liposomes In Vivo*, 1153 BIOCHIMICA BIOPHYSICA ACTA 9-19 (July 1993)]**

<ul style="list-style-type: none"> <li>Rodrigueza '93 discloses the use of liposomes with a mean diameter of <math>70\pm 19</math> nm (LUV<sub>50</sub>-unilamellar), <math>125\pm 30</math> nm (LUV<sub>100</sub>-unilamellar), and <math>237\pm 90</math> nm (MLV<sub>400</sub>-multilamellar) to mobilize cholesterol from the peripheral tissues of non-atherosclerotic mice.</li> </ul>	<ul style="list-style-type: none"> <li>This article was authored by two of the inventors and published within one year of the priority date of the present application.</li> </ul>
<p><b><u>U.S. Patent No. 6,139,871</u></b></p> <ul style="list-style-type: none"> <li>Discloses compositions and methods using unilamellar liposomes having an average diameter of 100-150 nm for treating atherosclerosis.</li> </ul>	<ul style="list-style-type: none"> <li>This patent is not prior art because the priority date of the present application is March 4, 1994.</li> </ul>